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INFORMATION SHEET FOR RESEARCH PARTICIPANTS

You will be given a copy of this information sheet and a signed copy of your consent form to keep, should you decide to participate in the study.

Investigation of the metabolic effects of DuOdenal resurfacing on insulin resistant woMen wIth polycystic ovariaN syndrOme
The DOMINO Trial

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you do decide to take part, please let us know beforehand if you have been involved in any other study during the last year. You are free to withdraw at any time without explanation. Please be assured that if you decide not to take part this will not affect your clinical care in any way.

WHAT IS THE PURPOSE OF THE STUDY?

You have been invited to participate in this research study because you have polycystic ovarian syndrome and insulin resistance. This means that you do not have regular periods and the reason is that your body is not sensitive to its own insulin. Treatments that improve this sensitivity have been shown to help women with PCOS start having regular periods and eventually get pregnant.

The innermost layer (mucosa) of the duodenum (small intestine immediately after your stomach) releases hormones that control your insulin resistance. Evidence from a recent study showed that a procedure to heat the duodenum (duodenal mucosa resurfacing (DMR) procedure) was a safe and potentially effective procedure to improve Type 2 Diabetes and possibly insulin resistance. The DMR procedure uses a device manufactured by Fractyl Laboratories and has the CE mark for the treatment of metabolic diseases.

The purpose of this study is to evaluate how effective this procedure is in people like you in the treatment of PCOS, i.e. can it make you start having periods. We want to assess this effectiveness by comparing the procedure to a "sham procedure" where you receive the same follow up and care but the DMR procedure will not be performed. This means that if you take part there is a 50% chance you will not receive the DMR procedure, although you will be given intensive NHS lifestyle advice for weight loss and it may be possible that you could receive the DMR when the study finishes if the DMR is shown to be effective.

WHY HAVE I BEEN INVITED?

You have been invited because you have polycystic ovarian syndrome with few and irregular or no periods, a body mass index equal or greater than 30 kg/m^2 and insulin resistance.

You should not take part in this study if you:

- have Type 1 or Type 2 diabetes mellitus.
- have significant medical or surgical conditions, which in the opinion of the investigators, would either interfere with the study or potentially cause harm to the volunteer. These include:

- Previous gastrointestinal surgery that could affect the ability to treat the duodenum such as subjects who have had a Billroth 2, Roux-en-Y gastric bypass, or other similar procedures or conditions.
- History of chronic or acute pancreas inflammation, active hepatitis or active liver disease or chronic kidney disease.
- Symptomatic gallstones or kidney stones, acute cholecystitis or history of duodenal inflammatory diseases including Crohn's and Coeliac Disease.
- History of bleeding tendency, upper gastro-intestinal bleeding conditions such as ulcers, gastric varices, strictures, congenital or acquired intestinal telangiectasia.
- Use of anticoagulation therapy (such as warfarin) which cannot be discontinued for 7 days before and 14 days after the procedure.
- Use of clopidogrel, pasugrel, ticagrelor which cannot be discontinued for 14 days before and 14 days after the procedure. Use of aspirin is allowed.
- Persistent anaemia, defined as haemoglobin less than 10 g/dl.

- take any medicine that may affect the trial (such us oral steroids, metformin, thiazolidinediones, atypical antipsychotics, hormonal contraceptives, weight loss medication) or harm you.
- have other causes of anovulation (e.g. hypothyroidism, adrenal or pituitary disorders).
- more than 6 periods within the previous 12 months.
- current pregnancy or breastfeeding at screening or 6 months previously.
- smoking at screening or 6 months previously, active illicit substance abuse or alcohol excess.
- do not have access to a telephone.
- have donated blood in the last 3 months or intend to do so by the end of the study.

WHAT IS THE DEVICE BEING TESTED?

The treatment is delivered using the Revita System. This system consists of two parts, a tube and a console unit. The tube is attached to the console and is then introduced into the upper part of the gut (food pipe, stomach and duodenum). At the same time, a flexible camera called an endoscope is used to look inside the duodenum in a procedure called an endoscopy. First, the catheter is used to inject salt water (saline) into the inner layer of the gut wall to protect the underlying muscle. Second, the balloon at the end of the catheter is filled with hot water to heat the mucosa in the duodenum. This completes the treatment. The device is used to deliver a superficial and temporary injury (or ablation) to the surface layer of the duodenum before regrowth of this layer occurs.

DO I HAVE TO TAKE PART?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

Screening: If you agree to volunteer for this study you will first have a consultation with a doctor from the team that will ensure that you meet the inclusion criteria for the study and take a medical history, examine you, take basic blood tests (for example to look at your kidney and liver function), take a urine sample for a pregnancy test and perform an electrocardiogram to look at the structure/function of your heart. For this purpose your details will be registered with the Imperial College Healthcare NHS Trust. You will be asked also to do an oral glucose tolerance test. This involves drinking a sugar load of 75 grams, followed by blood sampling for 3 hours.

You will be asked to take Medroxyprogesterone to induce a menstrual bleed before the baseline visit. Medroxyprogesterone is used routinely in clinical practice for the same indication. The induction of the bleed will enable you to be studied at the same phase of your menstrual cycle as the other women taking part in the study.

Baseline visit: This will take place approximately 4 weeks before the intervention. Forty eight hours before you attend for the study visit you may be asked to refrain from alcohol and strenuous physical activity. This is so that they do not affect the results of the studies. You will be invited to attend the clinical research facility at Imperial London in the morning of your assessment. You will lie on a hospital bed for several hours while we test your body's ability to process glucose, and how sensitive your body is to insulin, using the "clamp" test. A nurse or doctor will use needles to insert a tube (called a "cannulae") into each arm vein; the needles will be removed but the cannulae will remain inside your veins and will be used to either draw blood samples from your arms or inject an isotope, dextrose (a sugar) and insulin into your body over the course of approximately 8 hours. The isotope is not radioactive and will not affect you in any negative way; it helps us determine how much glucose is being processed by your body. We will aim to keep your blood sugar in the normal range. In the very unlikely event that your blood sugar goes low, we will be able to correct this promptly by infusing more dextrose. In total up to 180 mls of blood will be taken (~36 teaspoonful). At the end of the study you will be given something to eat and drink, the cannulae will be removed and you can go home.

During/around the time of your stay with us we will also:

- measure your body weight and body fat
- measure your blood pressure and pulse
- collect a blood and urine sample to analyse your metabolic and reproductive profile
- do a urine pregnancy test
- ask you to complete a food diary 3 days before the visit and return to the investigators

If you are recruited at University Hospitals Coventry and Warwickshire NHS Trust you will be offered to have an optional metabolic study at the Human Metabolic Research Unit (HMRU) for body composition, energy expenditure and sleep study. You will be asked to attended fasting since 22:00 pm previous night.

On your visit, you would be invited to have a measurement of body fat in a special capsule ('BodPod') which only takes a couple of minutes to perform. Following initial fasting samples, a small plastic tube will be inserted into a vein in the arm (so that blood samples can be taken from this during the study). These samples taken during HMRU will be anonymised. They will be stored for 10 years and analysed by the clinical research team.

You would be invited to stay in the room for 24 hours. During this time, blood tests will be taken at pre-defined time-points and you will be monitored continuously (pulse and blood pressure). You will be able to leave the room whenever you want during this time, but leaving the room would invalidate the experiment and the study would therefore need to be discontinued. There will be at least one member of the research team on the Human Metabolism Research Unit throughout each study, and you will be free to communicate with them at any time using the in-built intercom device. Following the 24-hour study, you will be free to leave.

The research room on the Human Metabolism Research Unit is specially-designed, and hermetically-sealed to the outside environment. From analysing the air moving into and out of the research room, we will measure the gases that you breathe in and out. This will provide us with data on metabolic rate. All meals will be provided whilst you are inside the research room, and any dietary requirements will be respected and catered for. You would be invited to undertake some mild physical exercise for a few minutes whilst inside the research room, although this will only be requested if you are willing and able to perform this. In addition, we would also assess your sleep quality with a portable sleep machine whilst you are inside the research room, and our research nurse will explain to you how this works before you enter the room. You will be also provided with theatre scrubs to ensure clothing standardisation during the study, and you will be asked to have two urine pregnancy tests.

This metabolic study will take place at baseline and 6 months post-intervention follow-up.

Intervention

At your baseline visit you will be randomised (allocated randomly by a computer programme) to undergo either the duodenal mucosal resurfacing or the sham procedure. The intervention will be performed by a skilled endoscopist at Imperial College London NHS Trust or King's College Hospital NHS Trust. If the procedure takes place at King's College Hospital NHS Trust you will also be registered there. The research and clinical team will not know which type of intervention did you have, unless clinical need and procedure dictates the un-blinding of the clinical team (e.g. development of a complication). You will not know which group you are in until the end of the trial.

You will be asked to fast the night before the procedure. Prior to the procedure you will need to sign a separate consent form which we do for any patient coming for an endoscopy. The procedure will be done under general anaesthesia with an anaesthetist present. In the first stage of the procedure, an endoscope (a small camera) will be passed through your mouth and stomach into the duodenum. The doctor performing the procedure will make sure there are no abnormalities in these areas that would prevent the procedure from being possible. These include things like ulcers, narrowing (strictures) or anatomy that would make the procedure too difficult or unsafe to perform.

If suitable, a guide-wire will be placed under X-ray guidance into the duodenum before the DMR catheter is placed over the wire and into your duodenum. You will be draped with a lead vest during the procedure to reduce the exposure to radiation. If you are in the DMR group, the catheter is used to inject liquid into the inner wall of the duodenum. The balloon at the end of the catheter is then filled with hot water to heat (or ablate) the mucosal surface of the duodenum to complete the treatment. If you are in the "sham" procedure group, the DMR catheter will be placed in the small intestine but no liquid will be injected and the lining of the small intestine will not be heated by water.

After the procedure you will be monitored for a few hours and then allowed to go home. You should either use a taxi or have someone give you a lift home. You should not drive or use public transport.

Following the procedure, you will need to follow a low-calorie diet for two weeks. This will be a liquid diet and you will be given advice on how to consume it by the research team. After the two weeks you will undergo a lifestyle modification programme that will be delivered by a dietician and psychologist for 6 months. They will see you every month in group or individual sessions and offer advice on how to change your nutrition in order to lose weight.

Early post-operative visit: This will take place ~14 days after the endoscopy. The following assessments and procedures will be performed:

- Clinical assessment
- Body weight and body fat
- Blood pressure and pulse
- Blood tests: routine blood tests like the ones you underwent during screening
- do a urine pregnancy test
- Oral glucose tolerance test
- Complete a food diary 3 days before the visit and return to the investigators
- Adverse events

12-week mechanistic visit: The following assessments and procedures will be performed:

- Clinical assessment
- Body weight and body fat
- Blood pressure and pulse
- Blood tests: routine blood tests like the ones you underwent during screening
- do a urine pregnancy test
- Euglycaemic hyperinsulinaemic clamp as described above
- Oral glucose tolerance test
- Ask you to complete a food diary 3 days before the visit and return to the investigators
- Adverse events

Reproductive assessments weeks 12-24
During the duration of the study, information about self-reported menstrual bleeding will be collected.

The reproductive assessments that will be performed from weeks 12 to 24 will include:

- Weekly pelvic ultrasound scans: The ultrasounds will be either transabdominal or transvaginal depending on views obtained and your preference. If transabdominal, you will be asked to lie down on an examination couch and to lift your clothes to uncover your abdomen. The radiologist will put a clear gel on your skin. He/she will then move the transducer firmly but slowly across the skin of your abdomen. You should not feel any pain during the abdominal ultrasound, but you may feel some discomfort if you have a full bladder. In case of being transvaginal, the ultrasound will be probed about two or three inches into your vaginal canal. When the transducer is inserted into your vagina, you will feel pressure and in some cases discomfort. The discomfort should be minimal and should go away once the procedure is complete. If something is extremely uncomfortable during the exam be sure to let the doctor know.
- Measure serum reproductive hormones 7-10 days later.
- Once-weekly blood test to analyse the reproductive profile.

If you are recruited at University Hospitals Coventry and Warwickshire NHS Trust you will be offered to have this follow-up done at locally.

6-month clinical visit
The clinical assessments will include:

- Body weight and body fat
- Blood pressure and pulse
- Blood tests: routine blood tests like the ones you underwent during screening
- do a urine pregnancy test
- Adverse events
- The energy expenditure study follow-up will be conducted for those patients who have opted to have it done at University Hospitals Coventry and Warwickshire NHS Trust.

WHAT ARE WE TESTING?

We are trying to find out if the Fractyl Revita System™ in women with polycystic ovarian syndrome is better for insulin resistance and reproductive profile than the sham procedure and if so we want to understand the underlying mechanisms.

WHAT ARE THE SIDE EFFECTS AND RISKS OF TAKING PART?

There are certain residual risks associated with the use of the Fractyl Revita System™ and the DMR procedure.

Common:

- discomfort and bruising at the cannulae insertion sites.
- abdominal bloating and discomfort following the procedure.
- sore throat after endoscopy.
- diarrhoea

Infrequent:

- Narrowing of the small bowel after the procedure which would require another endoscopy to treat.
- Failure of the equipment leading to cancellation of your procedure.
- Your blood sugar can go low during the clamp test; this will be promptly treated by the research team if it happens

Rare or theoretical risks:

- Perforation (a tear in your GI tract).
- Pancreatitis (inflammation of your pancreas).
- Low blood sugars after treatment – your doctor will go through symptoms of this.
- the procedure of guiding the wire uses x-ray radiation. Radiation can damage the DNA and might cause cancer. The risks associated to this procedure are equivalent to the exposure of about one year of natural background radiation; the risk for inducing cancer is very small (1 in 12,500 or 0.008%) compared to the natural occurrence of cancer of 1 in 4.
- General anaesthesia risks: These are rare, occurring in less than 1 in every 10,000 cases. They include a serious allergic reaction to the anaesthetic (anaphylaxis), an inherited reaction to the anaesthetic that causes breathing difficulties, waking up during your operation – but this is rare, and the amount of anaesthetic given will be continuously monitored to help ensure this does not happen, and death – this is very rare, occurring in 1 in every 100,000 to 1 in every 200,000 cases

During the study, experienced doctors will be available at any time should you have any concerns. You will be provided with a mobile number that you can call 24 hours a day 7 days a week in case you develop any unusual severe symptoms and want to speak urgently to a member of the team (07710067018). If you suffer from any ill effects during the study you should report these to the doctors immediately. You may withdraw from the study at any time, without providing any explanation. If there are any unexpected side effects, the study will be stopped.

CAN I TAKE PART IF I AM PREGNANT?

Pregnant women must not take part in this study. All participants will be asked to have a pregnancy test at the beginning of each study visit in order to ensure that they are not pregnant before the study visit commences. Volunteers should have adequate contraception (e.g. “barrier” methods, intrauterine device (non-hormone releasing), or abstinence) for the duration of the study. Any woman who finds that she has become pregnant while taking part in the study should immediately tell her research doctor.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

You will benefit from frequent direct contact with our specialist team and an intensive lifestyle intervention. You will see our specialist dietician either in group sessions or as a one-to-one for a period of 6 month and be given information on healthy eating, reducing food intake and increasing physical activity. This will be provided to both groups to help them lose weight start having periods. In addition, if you have had the sham procedure you will be offered the DMR after they have completed the trial. Also, you will learn a lot about your body and reproductive pattern by taking part in the special tests of the trial. The data obtained from this study would help the researchers to understand more about your condition and eventually this could help other patients with the same condition.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue in the study you will be asked to sign an updated consent form. Alternatively, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study.

WHAT WOULD HAPPEN IF I LOST THE ABILITY TO CONSENT DURING THE COURSE OF THE STUDY?

In the unlikely event that during the course of the study you were no longer able to give your consent because you had lost the capacity to do so, the research team would withdraw you from the study and not perform any further testing on you. However, they would retain body fluid samples and personal data collected previously and would continue to use it for the purposes which you had already consented.

WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

Once the study has finished, the results of the study will be made available to you and/or your GP should you wish. If you have any problems immediately following the study, then you should contact one of the research doctors (07710067018).

WHAT IF SOMETHING GOES WRONG?

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Chief Investigator or the study team (07710067018). The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Compliance Office.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Imperial College London as Sponsor of this study will follow The EU General Data Protection Regulation ("GDPR") that became law in all EU member states on 25 May 2018. Please read the attached transparency document for more information (Version 1.0; Date 3rd July 2018).

If you wish to raise a complaint about how the Sponsor has handled your personal data, you can contact the Sponsor's Data Protection Officer, who will investigate the matter. If you are not satisfied with their response or believe the Sponsor is processing your personal data in a way that is not lawful, you can complain to the Information Commissioner's Office (ICO).

The Sponsor's Data Protection Officer is Robert Scott and you can contact him at robert.scott@imperial.ac.uk.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results are likely to be published within the 12 months following the study. Your confidentiality will be ensured at all times and you will not be identified in any publication. At the end of the study, the results can be made available to you and/or your GP should you wish.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

This study is being organised by the Department of Investigative Medicine, Imperial College London. Fractyl® is funding this study through its investigator initiated study programme.

WHO HAS REVIEWED THE STUDY?

This study has been peer reviewed by the Imperial College Peer Review Office (Imperial College Healthcare NHS Trust) and reviewed and approved by the London-Dulwich Research Ethics Committee.

CONTACT FOR FURTHER INFORMATION

If you experience any problems during the study, you may withdraw at any stage. You will also have direct emergency access, 24 hours a day, to one of the doctors involved in the study through mobile number 07710067018. The doctors may also be contacted through Dr. Alexander Miras secretary (020 8383 3242) during office hours. The hospital switchboard (020 8383 1000) holds the home and mobile phone numbers for all the doctors involved in the study and can contact them at any time outside normal working hours if necessary.

PAYMENT

You will receive £300 upon completion of the study as a reimbursement for your time and your travel expenses. If you are based outside the M25 you will also have your travel expenses reimbursed.

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Consent form
Investigation of the metabolic effects of DuOdenal resurfacing on insulin resistant woMen wIth polycystic ovariaN syndrome
The DOMINO Trial

The participant should complete the whole of this sheet him or herself
(please initial each statement if it applies to you)

I have read the Information Sheet for Research Participants Version ……., dated …….	☐
I have been given the opportunity to ask questions and discuss this study	☐
I have received satisfactory answers to all my questions	☐
I have received enough information about the study	☐
I understand that I am free to withdraw from the study at any time, without having to give a reason for withdrawing and without affecting my future medical care	☐
I agree to take part in this study	☐
I agree that my GP will be informed that I am taking part in the study	☐
I understand that the NHS, Imperial College London as sponsor and regulatory authorities may also review records as part of audit process	☐
I agree that my samples will be kept for 10 years and may be used for further analysis or in future ethically approved research projects	☐
I agree that my samples may be sent for analysis outside Imperial College London, the United Kingdom, to the European Union, USA or commercial companies. Anonymised samples of isotopic enrichment quantification will be transferred to the University of Surrey for analysis.	☐
I am aware that, in the course of the study, if I were to lose the capacity to consent I would be withdrawn from the study. However, the body fluid samples and personal information collected prior to this would continue to be used for the purposes to which I have consented. (This could include further research on the samples after the current project has ended.)	☐

I consent to being registered at the Imperial College Healthcare NHS Trust or King's College Hospital NHS Trust and for my personal information being kept securely on NHS Trust computers. This information will only be accessible to researchers directly involved in the study and staff processing reimbursement. ☐

I am aware that Imperial College London as Sponsor of this study will follow The EU General Data Protection Regulation ("GDPR") ☐

One copy of the consent form will be given to the patient, one copy will be stored in the trial master folder and another copy will be stored in the medical records.

Participant's signature……Date……..

(NAME IN BLOCK CAPITALS) ……

Investigator's signature……..Date……

(NAME IN BLOCK CAPITALS) ……